Testing the Neural Sensitization and Kindling Hypothesis for Illness from Low Levels of Environmental Chemicals

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Sensitization in the neuroscience and pharmacology literatures is defined as progressive increase in the size of a response over repeated presentations of a stimulus. Types of sensitization include stimulant drug-induced time-dependent sensitization (TDS), an animal model related to substance abuse, and limbic kindling, an animal model for temporal lobe epilepsy. Neural sensitization (primarily nonconvulsive or subconvulsive) to the adverse properties of substances has been hypothesized to underlie the initiation and subsequent elicitation of heightened sensitivity to low levels of environmental chemicals. A corollary of the sensitization model is that individuals with illness from low-level chemicals are among the more sensitizable members of the population. The Working Group on Sensitization and Kindling identified two primary goals for a research approach to this problem: to perform controlled experiments to determine whether or not sensitization to low-level chemical exposures occurs in multiple chemical sensitivity (MCS) patients; and to use animal preparations for kindling and TDS as nonhomologous models for the initiation and elicitation of MCS. — Environ Health Perspect 105(Suppl 2):539–547 (1997)

Key words: sensitization, kindling, mesolimbic, human, animal, time factors, low-level exposures, psychophysiology

Background

Sensitization is the progressive increase in the size of a response over repeated presentations of a stimulus (*1*). Time-dependent sensitization (TDS), a term suggested by Antelman (*2,3*), involves sensitization by the simple passage of time between initial and later reexposures to a stimulus. Thus, intermittency is an important time-related feature of stimuli that initiate sensitization as opposed to continuous exposures that initiate tolerance (*4*). Pharmacologic agents, direct electrical stimulation, and physical and psychological stressors can all initiate or elicit the amplified responses in TDS (*2,5,6,7*). Sensitization can interact with tolerance and with conditioning (*8–10*), but each of these processes can be distinguished from the other by proper experimental design (*8–10*). The mechanisms of sensitization are not fully understood but may involve persistent changes in neurotransmitters, receptors, and basic neural cellular functions (*5,6*). Sensitization of immune function can occur during TDS protocols (*11*), but neural rather than classical immunological changes appear to mediate TDS of neurobehavioral functions (*2,6,12*). For example, various investigators have blocked drug-induced sensitization in the central nervous system using excitatory amino acid antagonists (*13*), nitric oxide synthase inhibitors (*14*), protein synthesis inhibitors (*15*), or delta-opioid receptor antagonists (*16*). In TDS, the subcortical, dopaminergic mesolimbic pathways also may be involved (*5,6*). A special type of neural sensitization is kindling, in which periodic repeated electrical or chemical stimulation of brain limbic structures such as the olfactory bulb, amygdala, and areas of the hippocampus leads to permanent susceptibility to convulsions not seen upon initial stimulation (*17–22*).

Because most persons with multiple chemical sensitivity (MCS) do not have clinical seizure disorders, kindling per se is not the most apt model for their condition (*7*). However, nonconvulsive TDS, subconvulsive kindling and/or related neural sensitization processes (*7,18,20–23*) could provide an explanation for a puzzling feature of MCS, i.e., susceptibility to low levels of environmental chemicals that according to classical toxicological dose–response relationships should not occur (*24*). Convergent lines of evidence point to this possibility. First, a subset, though not all, of MCS patients has been found to have increased lifetime histories or comorbid histories of certain psychiatric disorders, specifically major depression, anxiety disorders, and somatoform disorders (*25–29*). Researchers in biological psychiatry have proposed for many years that the recurrent, long-term course of these conditions follows the pattern of a sensitized response in that progressively less severe life stress or eventually

This paper is based on a work group discussion at the Conference on Experimental Approaches to Chemical Sensitivity held 20–22 September 1995 in Princeton, New Jersey. Manuscript received at EHP 6 March 1996; manuscript accepted 6 December 1996.

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Abbreviations used: CNS, central nervous system; DSM, Diagnostic and Statistical Manual; EEG, electroencephalography; EMG, electromyography; ERP, event-related potential; MCS, multiple chemical sensitivity; MMPI, Minnesota Multiphasic Personality Inventory; POMS, Profile of Mood States scale; PTSD, posttraumatic stress disorder; SCID, Structured Clinical Interview for DSM; SCL-90-R, Symptom Checklist 90 (revised); TDS, time-dependent sensitization; TLE, temporal lobe epilepsy.

no stress at all is required to trigger later episodes of illness (*12,30*). Still others have reported increased histories of childhood abuse in certain MCS patients (*31*). Early abuse may trigger increased rates of posttraumatic stress disorder (PTSD) (*32,33*). PTSD is a condition of persistent hyperreactivity to salient stimuli and other environmental stimuli (e.g., startle to noise) for which TDS is a leading model (*2,34*). Rather than assume that MCS is merely a misattribution of psychiatric symptoms from those conditions, an alternative view would be that the psychiatric findings and the MCS are both the result of an increased susceptibility to sensitization (*7,22*).

The second line of evidence that could provide an explanation for some patients' susceptibility to low levels of environmental chemicals is that other characteristics of TDS and MCS overlap (*3,5,7,22,35–37*). For example, females are more susceptible to both TDS and MCS (*38*). Both processes can be initiated by a wide range of chemically unrelated agents (*3*). Agents of different types can cross-sensitize with one another (*2,3,5*). Elicited responses can proceed in a bidirectional manner (*39,40*). The amplified responses can occur in multiple different bodily systems (*2,3,5,17*). Individuals sensitized through TDS and those with MCS can appear no different from the normal population in their responses to a given agent (*a*) at an initial but not later exposure (*41*); (*b*) at later exposures if insufficient time has passed since the last sensitizing exposure (*6,42*) (i.e., sensitization may not yet have occurred or is obscured by tolerance); (*c*) at later exposures if encountered under novel conditions different from those under which the original sensitization developed (*8,43*). An important implication of the latter points is that it will be essential to perform multiple, not one, exposure sessions separated in time to test the sensitization model for MCS (*7,22,36*). That is, it is necessary to initiate and elicit sensitization within the same experiment (*42*). Otherwise, negative findings could be explained as a lack of preexisting sensitization or as a suppression of a truly sensitized response by tolerance or by the novelty of the experimental situation at the time of a single test session.

Experimental Design—Human Studies

Participant Selection

Demographic variables important to MCS research include gender, age, education, and occupational/chemical exposure histories. The Working Group on Sensitization and Kindling concluded that research in MCS needs a generally accepted structured interview based upon common patterns of patient symptoms. Such an interview would help characterize the nosology of MCS and facilitate comparison of results between studies. It is feasible and reasonable to borrow from the precedents of mainstream psychiatry that generated the standardized *Diagnostic and Statistical Manual* (*DSM*)(*44*) and its associated *Structured Clinical Interview for DSM Diagnosis* (*SCID*)(*45*). These systematic tools for psychiatric diagnosis rely on patient self-reports of particular patterns of symptoms; determination of clinician agreement over etiological factors is not required for most diagnoses except for those related to specific drugs of abuse or organic causes such as a recognized medical condition. If and when generally accepted objective markers for MCS become available, specific test parameters can be incorporated into the overall case definition. This does not imply that MCS is or is not a psychiatric disorder. Rather, use of a phenomenologically based interview would capture the state of knowledge in the field at that time in a practical way so as to advance understanding of the problem.

Chronicity of illness would be important to establish, e.g., 6 months or longer, to eliminate persons with self-limited acute or subacute toxic reactions to accidental poisonings. The MCS interview items also should draw upon the descriptive scientific data beginning to emerge from surveys of patients (*46*) and the clinicians who evaluate them (*47–51*). For example, the number of incitant chemicals and severity of illness attributed to chemicals, regardless of the specific symptoms, may help distinguish MCS from overlapping syndromes such as chronic fatigue or fibromyalgia (*47*). Another important subtyping question might ask for self-identification of a defined initiating chemical exposure, including age at onset versus no clear onset date or event (*51*). Marked changes in lifestyle attributed to chemical sensitivity (*26*) are also distinguishing features of clinical MCS, including disability or change in occupation, personal hygiene products, places frequented or traveled to, home structure, and furnishings (*46*). Queries about specific symptoms might include the most frequent MCS complaints, e.g., feelings of unreality, memory difficulties, dizziness or lightheadedness, problems focusing eyes, muscle aches, tingling in fingers and/or toes, tiredness, irritability (*46*). Clinically, most MCS patients report additional intolerances to common foods and various medications (*46,52*).

One potentially important set of subtyping questions would be about past and/or current history of certain psychiatric disorders (*51*). For those items, the MCS interview might borrow the screening questions for past and current depression, anxiety disorders, and somatization disorder from the psychiatric SCID or other validated instruments [e.g., somatization screen (*53*); Minnesota Multiphasic Personality Inventory (MMPI) (*54*); Symptom Checklist 90, revised (SCL-90-R) (*55*)]. For instance, one could have dementia with or without comorbid depression (*44*). Similarly, available data indicate that one could have MCS with or without comorbid depression or anxiety disorders (*49–51*). Preliminary electroencephalographic studies by Bell et al. (*56*) indicate that the electrophysiological activation patterns of individuals with both chemical intolerance and depression differ from those of persons with only one or the other condition or neither. Thus, it may be essential to recruit subjects systematically who have or do not have specific features. Subject screening should include validated self-report and observer-rated measures of depression and anxiety, with specific cut-off scores for inclusion and exclusion criteria. Self-report measures could include instruments such as the Beck Depression Inventory (*57*) and the Spielberger State-Trait Anxiety Inventory (*58*); observer-rated measures could include the Hamilton Depression and Hamilton Anxiety Scales (*59*). By the same token, control/comparison groups, e.g., depressives or panic disorder patients, would have to be screened specifically to eliminate those with high levels of chemical intolerance. Preclinical or clinically mild chemical intolerance with minimal associated lifestyle changes is common in nonindustrial samples (*60–67*). However, previous controlled studies generally have not screened for chemical intolerance, thereby adding a major design flaw into comparisons of MCS patient groups with other groups such as medically ill patients or even some normal persons. A central tenet of experimental design is to select groups that differ on the key independent measure under consideration, e.g., degree of self-reported chemical odor intolerance.

Because of the lack of previous human studies in this area using specific outcome measures with chemical exposures, it is difficult to predict the appropriate group sample sizes to ensure adequate statistical power with certainty. However, sample sizes in the several studies that have demonstrated significant sensitization or failure of habituation of autonomic variables in human subjects have fallen in the range of 9 to 25 subjects per group (*42,68,69*). The ability to detect significant group differences in these between-group studies with these small samples suggests large estimated effect sizes. Similarly, animal studies of chemical sensitization with behavioral end points have used 9 to 32 animals per group (*5,20,70*). A between-subjects design in human studies could risk Type II error from insufficient sample size and too low power to detect medium- or small-sized effects. Nonetheless, the high likelihood of carryover effects from one exposure condition to another in a within-subjects design favors using a between-subjects approach. If within-subjects designs are used, a counterbalanced order of exposure conditions in separate subgroups of each group, e.g., MCS and controls, would assist in clarifying any such asymmetric transfer of effects (*71*). It will be necessary to restrict the number of outcome measures in any given protocol to limit confounding of results of one outcome measure by a preceding outcome measure (*72*).

An additional consideration for experimental design is that of stimulus range effects (*73*). The range of stimuli or the range of responses used by the subjects may affect their responses (*73*). That is, sensitization studies within subjects would risk confounding by range effects if a given subject were to undergo more than one experimental condition. This problem again favors the use of separate groups for each concentration, stressor, and time factor. The nature of sensitization studies requires use of repeated sessions with the same outcome measure(s) in the same subjects, but the experimental condition (i.e., chemical vs sham exposures) and the timing of exposures must differ among subgroups of each group. Taken together, these issues point to the need for a large number of separate groups in human or animal sensitization studies to be certain of the source of a given finding. For example, Antelman et al. (*74*) used nine separate groups rather than the same group of animals (n = 6–10 per group) to evaluate the effects on mesolimbic dopamine status of pretreatment with a range of different intensity environmental stressors (home cage, clean cage, dirty cage, black box) interacting with a range of drug treatment conditions (no injection, saline injection alone, or 0.2 mg/kg haloperidol in saline given at three different time lags after the pretreatment: none, 2 hr, or 2 weeks). They also used entirely separate groups of animals to confirm the stressfulness of each of the pretreatment conditions with glucocorticoid measurements. It also may be necessary to consider similar separate studies and between-groups methodology in human sensitization studies (*71–73*).

Experimental Conditions

Among many potential issues in the design of human MCS/sensitization studies are the following: state of adaptation or deadaptation of subjects (*24*); route of sensitizing and test exposures (e.g., oral, inhalation, dermal); environmental context (novel versus familiar). For the first issue, Ashford et al. (*75*) and Miller (*76*) have presented a systematic case for the need for an environmentally controlled medical unit where human subjects could be cleared of possible masking, adaptation, and/or pharmacological cross-tolerance to multiple inhaled chemicals. The sensitization working group agreed that one design for protocols to initiate and test for sensitization in MCS patients could involve the same sensitization procedures but compare outcomes under conditions of masking and unmasking.

Related to the second issue, route of sensitization, laboratory sensitization in animals has been initiated primarily by injection with drugs or pesticides (*3–6,19,20*) and inhalation with solvents such as toluene (*21,70*). In human studies, oral alcohol ingestion has been used successfully to initiate and demonstrate autonomic nervous system sensitization of nonalcoholics without first withdrawing them from alcohol outside the laboratory (*42*). The working group discussed the possibility of separate human studies involving different types of agents and routes of administration, e.g., oral ingestion of a drug such as methylphenidate or inhalation exposure to a solvent such as toluene. The advantage of testing for drug sensitization is the greater potential control over cross-sensitizing or cross-tolerant exposures outside the laboratory. From an ethical perspective, using a stimulant drug such as methylphenidate versus a placebo in humans would be a clinically appropriate trial. Current standards of practice in psychiatry indicate that low-dose stimulants may particularly benefit persons with low energy or depression related to medical conditions (*77*).

A test of stimulant sensitization in MCS patients and controls also would facilitate understanding of the question of the presence or absence of heightened general sensitizability in MCS patients, even though it would not directly address the involvement of specific environmental chemicals. Alternatively, the group considered other agents such as opiate drugs, substance P, or alcohol for possible tests of TDS. For example, Antelman (3) noted that human sensitization of β-endorphin to interleukin-2 has been shown in clinical populations (non-MCS) (*78*). Bell et al. (*79*) also have evidence that specific foods might induce sensitization of β-endorphin in nonclinical chemically intolerant elderly. Another important advantage of using drugs to test for TDS would be to evaluate the capacity of selected outcome measures under consideration for chemical exposure studies to exhibit sensitization. Repeated drug administrations would permit refinement of these outcome measures during administration of better studied agents at doses with known effects compared to possibly arbitrary selections of test chemicals and concentrations for initial chemical exposure studies.

In the case of inhaled volatile exposures in the laboratory as sensitizing events, one approach could mimic elements of the dose selection procedures used in Molhave et al (*80*). Different subgroups could receive various doses, e.g., low doses: subolfactory levels of a given substance (e.g., toluene) or volatile mixture (e.g., Molhave volatile organic compound mixture found in indoor air) in an exposure test chamber; moderate doses: detectable levels of a substance or mixture similar to those measured in sick buildings; high doses: detectable levels but below Occupational Safety and Health Administration (OSHA) standards for an industrial workplace. The duration of dosing would be important. Antelman (2) emphasized that brief exposures to a sensitizing agent may be more effective at initiating just sensitization and not tolerance, whereas prolonged exposures may tend to induce both sensitization and tolerance. Thus, studies could compare exposure durations of several minutes, 1 hr, or 6 to 8 hours at a time.

With regard to the third issue in the design of human sensitization studies, environmental context, Bell et al. (*36*) have extensively discussed the contextual points involved in sensitization research. These are relevant to ethical concerns to avoid persistent injury to subjects' health outside the laboratory setting. One way to approach these concerns would be to initiate human subjects in a context-dependent rather than independent manner (*9,42,81,82*). That is, the protocol for initiating sensitization would require that the physical setting (e.g., distinctive laboratory appearance, color of walls, etc.), procedures, and time of day be identical for both sensitization and testing sessions. Varying the context in which sensitization occurs could induce context-independent sensitization such as may relate to MCS patients' heightened chemical reactivity in a wide range of environments different from that of the originally identified exposure event. In contrast, the proposed laboratory procedures would require that the context remain the same throughout the study in order that the risk of subjects later reacting adversely be confined to reexposures during any return visits to the laboratory situation and not to other situations in their everyday lives. Thus, while context-dependent designs would help address ethical concerns for human studies, these same issues make it imperative that full testing of the sensitization hypothesis for MCS employ animal models to permit initiation and assessment of context-independent sensitization, i.e., administer the agent in various cages and/or rooms throughout the study.

The basic protocol for initiating and testing for context-dependent sensitization in human subjects would then involve at least two and preferably three or more laboratory sessions well spaced in time. The time interval between sessions for initiating TDS could range from 1 to 14 days. Testing immediately after a daily protocol in animals often does not reveal the sensitization (*6*). Past research suggests that it would then be necessary to wait at least several days, preferably 7 to 14 days, after the final sensitizing exposure to test for development of a sensitized response. While context-dependent designs by definition invoke elements of classical conditioning to the environment, it is still possible to design studies to differentiate sensitization from conditioning. For example, drawing from similar animal research (*9*), it would be possible to establish the development of an amplified response in humans to a given substance with a sensitization protocol, then repeatedly reexpose them to the same setting and procedures with sham exposures (e.g., arrowroot starch-filled capsules for drug placebo or filtered airstreams for inhalation route) until the amplified response returns to baseline, i.e., extinguishes. Then another test exposure with the active agent is conducted to see if the amplified response returns immediately. If so, then sensitization and conditioning factors have been separated; that is, the sensitized response is still present (elicitable) even though the conditioned, context-dependent component of the response is not (*9,10*).

Another variation of the contextual design that demonstrates the context-dependence would be to initiate laboratory sensitization to a given substance in a particular room of the laboratory and then test for TDS by reexposing half of each group to the same substance in the original exposure room and half of each group to the same substance in a distinctively different exposure room. Because novelty is expected to dampen the size of a sensitized response in context-dependent TDS (*8–10*), it is predicted that the sensitized group(s) would show a lesser response to the substance in the new room compared with that in the old room. However, retesting in the old room should reinstate the amplified response promptly. Various between-groups and within-groups crossover designs (e.g., ABABAB) counterbalanced for order of test room type (new or old) could be utilized [(*71–73*) however, on unwanted within-subjects effects]. Another possible strategy for addressing the ability of novelty to dampen elicitation of sensitization responses would be to habituate subjects to the laboratory setting and procedures for several sessions without chemical or drug exposures before beginning the sensitization process.

Dependent Variables

One of the least discussed but most important methodological issues in MCS research is the selection of outcome measures. Many investigators have elected relatively insensitive designs involving subjects' dichotomous guesses about the presence or absence of a chemical and/or subtle increases in subjective symptoms. While this approach may be especially important in the clinical situation and should be included in any human study, the Sensitization Working Group considers it necessary but not sufficient for the research situation. Dependent variables that would add objectivity and sensitivity to experimental design would include neurophysiological (e.g., olfactory-evoked potentials, cognitive event-related potentials [ERPs] such as P300, quantitative electroencephalography [EEG], and polysomnography) (*83–87*); neuroimaging (e.g., functional MRI); autonomic (e.g., pupil response, heart rate, blood pressure, respiratory, pulmonary function tests) (*68,69*); cognitive (e.g., continuous performance tests, divided attention tests, information-processing tests) (*88–90*); behavioral (e.g., Profile of Mood States [POMS] scale, anxiety sensitivity index) (*79,91*); and motor activity (e.g., physical activity monitors, facial electromyography [EMG] for positive and negative affect, acoustic startle responses) (*42,64*).

There are several advantages to most of the above measures. First, most of the variables can detect subtle and/or rapid changes in function as well as failure to habituate upon repeated sampling (*68*). Second, all variables except neuroimaging are relatively inexpensive and noninvasive to obtain repeatedly once the equipment has been purchased. These measures have been and currently are in use in scientific studies of human subjects with cognitive, affective, or somatic symptoms similar to those reported in MCS, e.g., dementias, depressions, PTSD, chronic pain, migraine headache, irritable bowel. Thus, the available research literature using those same measures would offer information on the specificity of any findings in MCS compared with findings for better characterized disorders.

Finally, testing the sensitization hypothesis in human subjects involves important methodological considerations. Design issues that pertain to TDS studies can differ from those used when testing other hypotheses for MCS. For example, the seemingly reasonable approach of pretesting with open challenges (*75*) of possible active and placebo substances to determine current reactivity or nonreactivity in MCS is not possible from a TDS perspective. Even in animal studies, prior experience with a stimulus changes a given individual's responsivity to later reexperiences if the individual is sensitizable (*2*). Thus, lack of initial reactivity to a particular substance does not necessarily predict lack of subsequent reactivity (*2,3,5,6,41*). Indeed, many different agents and stimuli evoke no difference in the first session of TDS studies between animals that will eventually sensitize and those that will not. A placebo at the beginning of an experiment could turn into an active agent in a sensitizable subject by the end of testing

For this reason, most animal TDS studies utilize between-group rather than within-group designs (*2,5,6*). For example, one of several control groups proceeds through the experiment with no exposures to the test agent. Another control group receives the test agent only at the final testing session. In comparison, the experimental group(s) receive the test agent repeatedly at each sensitizing session and at the final testing session. In addition to designs using different initiating exposures, another design strategy is to compare groups of animals predicted to exhibit individual differences in sensitizability. Such groups would include different genetic strains (*92*), females versus males (*93,94*), or hyperreactivity versus hyporeactivity to novelty (*41*). That is, half the animals are predicted to be maximally, and half to be minimally, sensitizable. For human studies, selection of control groups to compare with MCS patients might mean ensuring that such groups lack potential for sensitizability, e.g., no family histories of recurrent affective disorders or substance abuse (*65*), as well as no self-reported chemical odor intolerance.

In summary, the working group suggests two primary experimental approaches, one involving a shorter-term repeated measures design, the other involving longitudinal follow-up of persons who had experienced an identifiable chemical exposure event. The first study would compare MCS patients with any of various control groups for initiation and elicitation of sensitization to low-level chemical exposures. The second study would determine risk factors for developing MCS by assessing persons who later develop MCS and those who do not.

Experiment 1, Repeated Measures Study

The first study would test the hypothesis that MCS patients are more susceptible to initiation of context-dependent sensitization than control subjects. This short-term between-subjects sensitization study (over a period of 6 weeks, one session per week) would involve three sessions of habituation to the laboratory and procedures but without chemical exposures followed by three test sessions (active or placebo). Pilot studies should include pretesting the sensitivity of proposed outcome measures to sensitization in normals (who then would not participate in any other part of the research) to an agent such as methylphenidate; and determination of olfactory thresholds in MCS patients and controls (who then would not participate in any other part of the research) for active chemical agents used in the study. For the primary study, participants would include MCS patients with and without depression and nonchemically sensitive controls with and without major depression. The study will purposely oversample women to approximate the reported gender distribution among MCS sufferers (*24*). In view of the animal evidence that a high estrogen-to-progesterone ratio might favor sensitization in females (*93*) and that testosterone might lessen sensitization in males (*94*), an adjunctive exploratory measure for risk of sensitization in this human study might be blood levels of estrogen and progesterone at specified times in the menstrual cycle as well as blood levels of testosterone.

From the above list of possible dependent variables, an initial selection might include physiological measures considered most likely to detect group differences, i.e., stabilometer (general motor activity level), respiration, heart rate, pupil, EEG and cognitive event-related potentials (auditory odd-ball paradigm), and facial EMG (an objective and sensitive correlate of mood state). For mood changes and cognitive dysfunction respectively, the POMS and specific neuropsychological tests previously found to show differences from those of controls in studies of chemically intolerant or solvent-exposed persons (e.g., divided attention, continuous performance test) would be appropriate (*85,89,95*).

All participants would undergo initial baseline sessions on filtered room air delivered by an olfactometer similar to that used by Kobal and Hummel (*83*) to facilitate habituation to the novelty of the laboratory and procedures. For subsequent sessions in this study, an olfactometer would deliver brief exposures to filtered room air (the placebo) and test chemicals (e.g., subolfactory and supraolfactory threshold levels of toluene in air stream) (below and above threshold). Half the participants in each group would get filtered room air during the entire experiment and half of each group would get the chemical (split-plot design). The exposure would occur as either intermittent bursts (1-min exposure, 3-min wait) or continuous exposures for at least 10 to 15 min. Additional sessions would occur at 1-, 2-, and 3-week intervals at the same time of day.

While studies designed to elicit acute adverse reactions in MCS patients raise ethical concerns, the need for systematic understanding of this illness and its mechanisms is pressing. Lack of data has severely hampered research on possible preventive and treatment interventions. At the present stage of knowledge about MCS, the potential benefits outweigh the risks. That is, acute reactions in chemically sensitive individuals typically resolve within minutes to hours after conclusion of a low-level chemical exposure. Most patients do not experience life-threatening symptoms during such reactions, and those with disorders such as asthma or epilepsy can be screened out of the studies. However, even in standard clinical practice, diagnostic testing for conditions with episodic rather than continuous clinical manifestations, e.g., methacholine challenge in asthma or hyperventilation during EEG recording in epilepsy, often involves deliberate provocation of acute exacerbations as part of a workup. The laboratory context-dependent design of the present proposed experiments would minimize the risk of persistent worsening of a patient's long-term course, as discussed above. Thus, it is reasonable to proceed with acute chemical exposure research in MCS at this time. The emergence of new data in the area may or may not necessitate reassessment of the ethics of additional challenge studies in the future.

Experiment 2, Longitudinal Study

In addition to acute studies, longitudinal studies with repeated measures would permit evaluation of fluctuations over time in MCS, which is inherently a chronic condition (*48*). As indicated above, studies of sensitization require repeated measure designs. Ethical concerns in human research obviously preclude any experimental effort to initiate MCS in healthy persons. Rather, participant samples for a longitudinal study would include individuals either with preexisting MCS or with a history of an acute identifiable toxicant exposure (cohort of persons who proceed over time to develop or not develop MCS). This approach takes advantage of preexisting conditions in affected persons, and involves repeated evaluations of symptoms, mood, electrophysiological and autonomic status, and cognitive performance. The use of these outcome measures does not appear to raise any ethical concerns, as they would monitor but not alter the course of MCS patients' illnesses. Nonetheless, these measures might reveal evidence of a sensitized state in MCS patients [compare Morrow and Steinhauer (*68*)]. In addition to descriptive data on the course of MCS, a longitudinal study would test the hypothesis that MCS patients but not healthy similarly exposed individuals show maintenance and/or progression of sensitization in measures of nervous system dysfunction over extended periods of time, following induction by an initial toxic exposure or other event.

Periodic laboratory reevaluations would permit assessment of progressive change (e.g., worsening, improvement, plateau) or persistence of change over extended blocks of time [e.g., seven or eight times on an every-6-months basis during a 5-year study, compare Morrow and Steinhauer (*68*)]. Monthly laboratory evaluations would entail excessive subject burden and risk; however, the working group recommends monthly telephone follow-up data collection. Outcome variables on which the telephone component could focus include a POMS, an individualized symptom-rating scale for frequency and severity, updates on medical/psychiatric diagnoses and treatments, and a quality-of-life questionnaire. Six-month laboratory follow-ups could include specific variables such as cognitive, affective (POMS, MMPI), and physiological (ERPs in response to the challenge). If a component of the study assessed MCS in its adapted versus nonadapted state to obtain continuous physiological recordings, an inpatient study in an environmental medical unit would be necessary.

Overall, this model encompasses both the possibility of individual differences between MCS patients and normal patients in general sensitizability and cross-sensitizability to different agents and classes of stimuli and the possibility of differences between chemical agents in their abilities to initiate and elicit sensitization in persons with equivalent degrees of sensitizability. Studies designed to evaluate each of these areas may be needed to provide a complete test of the model.

Animal Studies

Rationale

If a kindlinglike process or neural time-dependent sensitization is a mechanism that underlies MCS, direct olfactory stimulation probably represents the most likely route of exposure (*21,96–98*). Although inhalation exposures through the lung obviously occur simultaneously with olfactory system stimulation, and although the inhalation route may play some role in modulation of neural sensitization, the concentration of inhaled chemicals reaching the brain from nonolfactory routes of administration probably is not sufficient to cause the kinds of neural activation necessary to support a kindlinglike process (*98*). Accordingly, although bloodborne chemical contaminants may contribute to some systemic chemical kindlinglike effect, if a neural sensitization process is involved in the development of MCS, it is more probable that the process involves the output from stimulation of the olfactory apparatus (*96–101*).

Olfactory pathways, specifically the olfactory bulbs, are particularly sensitive to electrical and chemical kindling (*21*). Additionally, the receptors in the olfactory epithelium form a direct access pathway to limbic structures in the central nervous system. It is reasonable, therefore, to assume that strong activation of the olfactory epithelium cells can provide sufficient input into CNS limbic circuits to induce sensitization. It probably is possible to design studies that indirectly test this hypothesis using human subjects, but the specific role of olfactory stimulation in the ontogeny of MCS can be directly evaluated using standard neurophysiological assessments of central olfactory and limbic structures in response to stimulation of the olfactory epithelia of laboratory animals (*21*).

Experimental Procedures

The following procedures test the hypothesis that repeated olfactory exposures to chemicals can modulate neurophysiological activity in the olfactory–limbic axis or that neurophysiological activity in the olfactory–limbic axis can be modulated using techniques such as footshock-induced stress, partial limbic kindling, or psychostimulant sensitization, which have been implicated in physiological or behavioral sensitization.

Experiment 1. The most direct test of an olfactory system-mediated sensitization process involves the monitoring of olfactory–limbic neural activity during and after repeated stimulations of the olfactory epithelium with compounds implicated in the initiation of MCS. Although it is probable that CNS olfactory activity has been assessed after chemical stimulation of the olfactory epithelium, it is improbable that structures other than the olfactory bulb have been studied, and that the olfactory bulb recording studies that have been conducted have assessed long-term changes in neural functioning after systematic repetitive chemical stimulations.

Paradigm. Microelectrode bundles will be chronically implanted into the olfactory bulbs, the pyriform cortex, the hippocampus, the entorhinal cortex, the amygdala, the medial hypothalamus, or the ventral tegmental area. The olfactory epithelium will be stimulated with vapors from chemicals believed to initiate MCS, vapors from chemicals not usually reported to initiate MCS, or distilled water vapor six times in a 2-hr testing session at equally spaced 20-min intervals. Exposure procedures for inhaled vapor generation will be adapted from Wood et al. (*102–103*). Unit firing patterns will be assessed from each of the microelectrode bundles during stimulation for a period of 15 min following cessation of stimulation. Testing sessions will be conducted daily for 15 days. In addition, to test for changes that may occur after the passage of time, animals will be tested 30 and/or 60 days later.

Experiment 2. Genetic or other predisposing variables may account for an innate predisposition for induction of sensitization in persons who present with symptoms of MCS. If this is true, it is possible that sensitization arising from direct olfactory stimulation may not specifically induce limbic sensitivity in normal (i.e., nonsensitivity-primed) rats. The following experiment tests the hypothesis that exposures to initiating chemicals can modulate neurophysiological activity in the olfactory–limbic axis in rats that have undergone experimental manipulations previously demonstrated to result in neural sensitization.

Paradigm. Rats will be implanted with microelectrode bundles and groups of animals evaluated for baseline chemically induced firing patterns using the same procedure as in Experiment 1. The animals will be sensitized by one of the following procedures: footshock stress-induced sensitization; partial amygdala kindling; or psychostimulant sensitization. Neural responses to chemical olfactory stimulation will be reassessed following induction of sensitization.

Experiment 3. It is possible that an interaction exists between repeated olfactory stimulation and other sensitization induction processes in which sensitization induced by some other physiological process (e.g., stress) is exacerbated by prior repeated olfactory stimulation. The following experiments test the hypothesis that repeated exposure to chemicals can alter sensitization parameters in experimental manipulations previously demonstrated to result in neural sensitization.

Paradigm. Groups of rats will be exposed to chemicals as in Experiment 1 over 15 trial days. Following the olfactory stimulation procedure, the rats will be sensitized by the procedures described in Experiment 2. Latency or number of trials required to induce sensitization are then compared.

Conclusions

The Working Group on Sensitization and Kindling agreed that a neural sensitization hypothesis for initiation and elicitation of MCS is testable in both human and animal experiments. Both kinds of experiments are essential to provide a full test of the hypothesis and, in animal research, to permit further elucidation of underlying mechanisms. The public health implications of chemical intolerance or chemical sensitivity are potentially extensive. A problem such as chemical odor intolerance, reported at subclinical degrees by at least 15% of American nonindustrial populations, e.g., young adults (*61,64,65*) and active community elderly (*62,63*) as well as by 30% of office workers (*67*) and of a rural community-based population (*66*), merits systematic investigation of its phenomenology, course, and possible mechanisms.

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